SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Prosthesis, Intervertebral Disc
Device Trade Name:	PRODISC®-L Total Disc Replacement
Applicant's Name and Address:	Synthes Spine 1302 Wrights Lane E. West Chester, PA 19380
Premarket Approval Application (PMA) Number:	P050010
Date of Notice of Approval of Application:	August 14, 2006

II. INDICATIONS FOR USE

The PRODISC®-L Total Disc Replacement is indicated for spinal arthroplasty in skeletally mature patients with degenerative disc disease (DDD) at one level from L3-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients should have no more than Grade 1 spondylolisthesis at the involved level. Patients receiving the PRODISC®-L Total Disc Replacement should have failed at least six months of conservative treatment prior to implantation of the PRODISC®-L Total Disc Replacement.

III. CONTRAINDICATIONS

The PRODISC®-L Total Disc Replacement should not be implanted in patients with the following conditions:

- Active systemic infection or infection localized to the site of implantation
- Osteopenia or osteoporosis defined as DEXA bone density measured T-score < -1.0
- Bony lumbar spinal stenosis
- Allergy or sensitivity to implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)
- Isolated radicular compression syndromes, especially due to disc herniation
- Pars defect
- Involved vertebral endplate that is dimensionally smaller than 34.5mm in the medial-lateral and/or 27mm in the anterior-posterior directions
- Clinically compromised vertebral bodies at the affected level due to current or past trauma
- Lytic spondylolisthesis or degenerative spondylolisthesis of grade > 1

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PRODISC®-L Total Disc Replacement labeling.

V. DEVICE DESCRIPTION

The PRODISC®-L Total Disc Replacement is a weight-bearing modular implant consisting of two endplates and one polyethylene inlay. The PRODISC®-L endplates are manufactured from cobalt-chromium alloy conforming to ISO 5832-12 (1996) "Implants for surgery – Metallic materials – Part 12: Wrought cobalt-chromium-molybdenum alloy" and are available in two sizes (medium and large). The superior endplates are also available in two lordotic angles (6° and 11°). The surfaces of both inferior and superior endplates are plasma sprayed with commercially pure (CP) titanium conforming to ISO/DIS 5832-2 (1999) "Implants for surgery – Metallic materials– Part 2: Unalloyed titanium." Fixation of the PRODISC®-L to the vertebral bodies is intended to be achieved through bony ingrowth, with initial stabilization by a large central keel and two small spikes on the surface of the two endplates. The inlays are manufactured from ultra-high molecular weight polyethylene (UHMWPE), and are available in three thicknesses (10, 12, and 14mm) with anterior-posterior and lateral sizing consistent with the endplate sizing. The inlay snap-locks into the inferior endplate and provides the inferior convex bearing surface that articulates with the concave bearing surface of the superior endplate. The range of motion allowed by the PRODISC®-L is 13° of flexion, 7° of extension, ±10° of lateral bending, and ±3° of axial rotation, as measured through *in vitro* testing.

Tables 1 and 2 describe the available sizes and configurations of the PRODISC®-L Total Disc Replacement components:

Table 1: PRODISC®-L Endplates

Size	Approximate Dimensions		Angles (degrees)
	Anterior/Posterior width (mm)	Lateral width (mm)	
Inferior Endplate – Medium	27	34.5	0 °
Inferior Endplate – Large	30	39	0 °
Superior Endplate – Medium	27	34.5	6 °
Superior Endplate – Medium	27	34.5	11 °
Superior Endplate – Large	30	39	6 °
Superior Endplate – Large	30	39	11 °

Table 2: PRODISC®-L Inlays

Size	Approximate Dimensions		Height (mm) (Assembled)
	Anterior/Posterior width (mm)	Lateral width (mm)	
PE Inlay – Medium	26	23	10
PE Inlay – Medium	26	23	12
PE Inlay – Medium	26	23	14
PE Inlay – Large	29	25	10
PE Inlay – Large	29	25	12
PE Inlay – Large	29	25	14

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Non-surgical alternatives to performing total disc replacement in the lumbar vertebral region include, but are not limited to, conservative treatment without intervention, medications, chiropractic care, disc injections, and/or physical therapy.

Surgical alternatives include, but are not limited to, surgical decompression, posterior lumbar interbody fusion (PLIF) procedures with or without posterior instrumentation, anterior lumbar interbody fusion (ALIF) procedures with or without posterior instrumentation, combined anterior and posterolateral (360°) fusion procedures, fusions using anterior/anterolateral spinal systems (e.g., plate and screw systems), or fusions using posterior spinal systems (e.g., pedicle screw/rod and hook/rod systems). In each case, the fusions would involve the use of autograft and/or allograft bone.

VII. MARKETING HISTORY

The PRODISC®-L Total Disc Replacement has been commercially available in markets outside of the United States since 1990. The device has not been withdrawn from the market for any reason.

USE OF THE PRODISC®-L IN OTHER COUNTRIES

Austria	Portugal	Malaysia	Italy	Costa Rica
Belgium	Spain	New Zealand	Netherlands	Ecuador
Luxembourg	Sweden	Singapore	Norway	Mexico
Czech Republic	Switzerland	South Korea	Poland	Venezuela
Denmark	Turkey	Argentina	Saudi Arabia	Hong Kong
Finland	Slovakia	Brazil	Israel	Germany
France	United Kingdom	Chile	Australia	Hungary
Iran	South Africa	Colombia	Thailand	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The PRODISC®-L Total Disc Replacement was implanted in 162 investigational subjects and outcomes were compared to those of 80 control subjects who received a circumferential fusion consisting of an interbody fusion using a commercially available femoral ring allograft and a posterolateral fusion with autogenous iliac crest bone graft, combined with pedicle screw instrumentation. Each investigational site was also required to enroll their first three PRODISC®-L Total Disc Replacement subjects as non-randomized cases, with a total of 50 non-randomized, training subjects enrolled. The investigational group was implanted with the device via an anterior surgical approach. The control group was implanted using a circumferential fusion technique.

The following adverse events were reported during the randomized, multi-center clinical study of 212 patients treated with the PRODISC®-L Total Disc Replacement (162 randomized and 50 non-randomized) and 80 control patients. **Table 3** lists adverse events that occurred in the control (F), randomized PRODISC®-L (P), and non-randomized PRODISC®-L subjects (PNR) and shows the time course distribution of the occurrence of the events. No deaths were reported.

TABLE 3 Time Course of All Adverse Events

	Intra-op 0-2 days			Peri-op >2-42 days			Short Term >42-210 days			Long Term >210 days			Number of Patients Reporting (%) and Total Events					
	F	P	PNR	F	P	PNR	F	P	PNR	F	P	PNR	Fusion (n=80)		ProDisc (n=162)		ProDisc-NR (n=50)	
													# (%)	Events	# (%)	Events	# (%)	Events
ALL ADVERSE EVENTS	29	49	12	23	48	10	39	67	18	41	97	25	70 (87.5%)	256	136 (84.0%)	505	41 (82.0%)	106
ANEMIA	2	4	0	0	2	0	0	0	0	0	0	0	2 (2.5%)	2	6 (3.7%)	7	0 (0.0%)	0
BURNING OR DYSESTHETIC PAIN	2	1	0	0	1	0	0	2	0	1	4	1	3 (3.8%)	3	8 (4.9%)	8	1 (2.0%)	1
CARDIOVASCULAR	2	1	3	0	0	0	0	0	1	3	1	1	5 (6.3%)	5	2 (1.2%)	2	5 (10.0%)	5
CLINICALLY SIGNIFICANT BLOOD LOSS (>1500 CC)	2	0	0	0	0	0	0	0	0	0	0	0	2 (2.5%)	2	0 (0.0%)	0	0 (0.0%)	0
DEGENERATIVE DISEASE PROGRESSION, NON-LUMBAR	0	0	0	0	0	0	0	1	0	0	2	0	0 (0.0%)	0	3 (1.9%)	3	0 (0.0%)	0
DEGENERATIVE DISEASE PROGRESSION, OTHER LUMBAR[1]	0	0	0	0	0	0	0	3	0	0	6	0	0 (0.0%)	0	9 (5.6%)	9	0 (0.0%)	0
DERMATOLOGICAL	1	1	0	0	2	0	1	1	0	0	2	0	2 (2.5%)	3	6 (3.7%)	6	0 (0.0%)	0
DERMATOLOGICAL DRUG ALLERGY	0	1	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	0	2 (1.2%)	2	0 (0.0%)	0
DIZZINESS	1	2	0	1	0	0	1	1	0	0	1	1	3 (3.8%)	3	4 (2.5%)	4	1 (2.0%)	1
DRUG ALLERGY	1	0	0	0	1	0	0	0	0	0	2	0	1 (1.3%)	1	2 (1.2%)	3	0 (0.0%)	0
DURAL TEAR	2	0	1	0	0	0	0	0	0	0	0	0	2 (2.5%)	2	0 (0.0%)	0	1 (2.0%)	1
EDEMA	0	0	0	2	2	0	1	3	1	0	3	0	3 (3.8%)	3	8 (4.9%)	9	1 (2.0%)	1
FEVER	7	8	2	3	2	0	0	0	0	0	0	0	10 (12.5%)	10	10 (6.2%)	10	2 (4.0%)	2
FRACTURE (NON-VERTEBRAL)	0	0	0	0	0	0	0	0	0	0	2	1	0 (0.0%)	0	2 (1.2%)	2	1 (2.0%)	1
GASTROINTESTINAL	14	21	6	3	6	2	3	3	0	3	5	1	22 (27.5%)	28	32 (19.8%)	45	8 (16.0%)	9
GENITOURINARY	1	6	0	1	2	0	0	3	1	2	3	1	4 (5.0%)	4	14 (8.6%)	14	2 (4.0%)	2
HEADACHE	1	7	0	1	0	0	1	1	0	2	3	3	5 (6.3%)	5	11 (6.8%)	12	3 (6.0%)	3
HERNIATED NUCLEUS PULPOSUS	0	0	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
INCONTINENCE	0	0	0	0	0	0	0	0	0	4	3	0	4 (5.0%)	4	3 (1.9%)	3	0 (0.0%)	0
INFECTION - OTHER NON WOUND RELATED	1	0	0	1	2	0	0	1	1	3	2	1	5 (6.3%)	6	5 (3.1%)	5	2 (4.0%)	2
INFECTION - SUPERFICIAL WOUND WITH INCISION SITE PAIN	0	0	0	1	0	1	0	0	0	1	0	0	2 (2.5%)	2	0 (0.0%)	0	1 (2.0%)	1
INFECTION - UTI	0	0	0	0	0	1	0	0	1	1	0	0	1 (1.3%)	1	0 (0.0%)	0	2 (4.0%)	2
INSOMNIA	1	3	0	1	0	0	1	3	0	1	2	1	4 (5.0%)	4	8 (4.9%)	8	1 (2.0%)	1
MIGRATION NOT REQUIRING SURGERY	0	0	0	0	0	0	0	3	2	1	0	0	1 (1.3%)	1	3 (1.9%)	3	2 (4.0%)	2
MIGRATION REQUIRING SURGERY	0	0	0	0	2	0	0	0	0	0	2	0	0 (0.0%)	0	4 (2.5%)	4	0 (0.0%)	0
MOTOR DEFICIT / INDEX LEVEL	0	0	0	0	0	0	0	1	0	0	4	0	0 (0.0%)	0	4 (2.5%)	5	0 (0.0%)	0
MUSCULOSKELETAL SPASMS - BACK	0	0	0	0	0	0	2	0	0	0	1	0	2 (2.5%)	2	1 (0.6%)	1	0 (0.0%)	0
MUSCULOSKELETAL SPASMS - BACK AND LEG	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.0%)	1
MUSCULOSKELETAL SPASMS - LEG	0	0	0	0	0	0	0	0	0	0	2	0	0 (0.0%)	0	2 (1.2%)	2	0 (0.0%)	0
NARCOTICS USE	0	0	0	0	1	0	1	1	1	0	0	0	1 (1.3%)	1	2 (1.2%)	2	1 (2.0%)	1
NERVE ROOT INJURY	0	1	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	0	1 (0.6%)	1	1 (2.0%)	1
NON-SPECIFIC MUSCULOSKELETAL SPASMS	1	3	0	0	3	0	0	0	0	0	1	0	1 (1.3%)	1	6 (3.7%)	7	0 (0.0%)	0
NUMBNESS INDEX LEVEL RELATED	0	0	0	0	0	0	1	0	0	0	0	0	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
NUMBNESS PERIPHERAL NERVE OR NON-INDEX LEVEL RELATED	0	3	3	1	1	1	4	9	0	0	6	1	5 (6.3%)	5	17 (10.5%)	20	5 (10.0%)	5
OTHER MUSCULOSKELETAL	1	1	0	0	1	1	6	9	0	7	17	2	13 (16.3%)	15	21 (13.0%)	28	3 (6.0%)	3
OTHER*	2	3	0	1	0	0	0	2	0	5	7	2	8 (10.0%)	8	11 (6.8%)	13	2 (4.0%)	2
PAIN - BACK	0	1	1	2	3	2	10	25	4	18	32	6	27 (33.8%)	33	55 (34.0%)	65	13 (26.0%)	14
PAIN - BACK AND LOWER EXTREMITIES	0	1	0	1	4	1	5	14	2	4	16	9	10 (12.5%)	10	29 (17.9%)	38	10 (20.0%)	12
PAIN - BACK AND LOWER EXTREMITIES WITH BURNING	0	0	0	0	0	0	0	1	1	0	2	1	0 (0.0%)	0	3 (1.9%)	3	2 (4.0%)	2
PAIN - BACK AND LOWER EXTREMITIES WITH NUMB AT INDEX	0	0	0	1	1	0	1	2	0	2	1	0	4 (5.0%)	5	4 (2.5%)	4	0 (0.0%)	0
PAIN - BACK AND OTHER	0	0	0	0	1	0	2	2	0	3	5	1	5 (6.3%)	5	8 (4.9%)	8	1 (2.0%)	1
PAIN - GROIN AREA	0	0	0	0	0	0	0	2	0	0	3	0	0 (0.0%)	0	5 (3.1%)	5	0 (0.0%)	0
PAIN - INCISION SITE	0	1	0	0	1	0	3	0	0	3	0	0	6 (7.5%)	6	2 (1.2%)	2	0 (0.0%)	0
PAIN - LOWER EXTREMITIES	0	1	0	2	9	4	8	15	3	6	13	2	16 (20.0%)	22	32 (19.8%)	40	8 (16.0%)	11
PAIN - LOWER EXTREMITIES WITH NUMBNESS AT INDEX LEVEL	0	0	0	1	1	0	0	1	1	0	1	1	1 (1.3%)	1	3 (1.9%)	3	2 (4.0%)	2
PAIN OTHER (NOT BACK/HIP/LEG)	2	4	0	3	7	1	2	7	0	5	14	1	12 (15.0%)	14	25 (15.4%)	37	2 (4.0%)	3
PRURITUS	2	7	2	2	1	0	0	0	0	0	0	0	4 (5.0%)	6	8 (4.9%)	8	2 (4.0%)	2
PSYCHOLOGICAL	1	5	0	0	4	0	1	2	0	4	10	1	6 (7.5%)	6	19 (11.7%)	20	1 (2.0%)	1
PULMONARY INFECTION	0	0	0	0	0	0	0	0	0	1	0	2	1 (1.3%)	1	0 (0.0%)	0	2 (4.0%)	2
RADIOLUCENCY - GRAFT	0	0	0	0	0	0	0	0	0	1	0	0	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
REFLEX CHANGE	0	0	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
RESPIRATORY	0	2	0	0	0	0	0	1	0	0	1	0	0 (0.0%)	0	4 (2.5%)	5	0 (0.0%)	0
RETROGRADE EJACULATION	1	0	0	0	1	1	0	1	1	0	0	0	1 (1.3%)	1	2 (1.2%)	2	2 (4.0%)	2
SUBSIDENCE NOT REQUIRING SURGERY	0	0	0	0	1	0	0	0	0	1	1	1	1 (1.3%)	1	2 (1.2%)	2	1 (2.0%)	1
SUBSIDENCE REQUIRING SURGERY	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
SURGERY - ADJACENT LEVEL	0	0	0	0	0	0	1	0	1	0	2	0	1 (1.3%)	1	2 (1.2%)	2	1 (2.0%)	1
SURGERY - INDEX LEVEL (REVISION)	0	1	0	0	0	0	1	0	0	3	0	0	4 (5.0%)	4	1 (0.6%)	1	0 (0.0%)	0
SURGERY - INDEX LEVEL (SUPPLEMENTAL FIXATION)	0	0	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
SURGERY - OTHER	0	0	0	1	0	0	2	1	0	0	6	3	3 (3.8%)	3	7 (4.3%)	7	3 (6.0%)	3
THROMBOSIS	0	0	0	0	0	1	0	0	0	0	0	0	0 (0.0%)	0	0 (0.0%)	0	1 (2.0%)	1
THROMBOSIS (DVT LEG)	0	0	0	1	2	0	0	0	0	0	0	0	1 (1.3%)	1	2 (1.2%)	2	0 (0.0%)	0
VESSEL DAMAGE/BLEEDING, MAJOR	1	1	0	0	0	0	0	0	0	0	0	0	1 (1.3%)	1	1 (0.6%)	1	0 (0.0%)	0
VESSEL DAMAGE/BLEEDING, MINOR	4	4	0	1	0	0	0	0	0	0	0	0	5 (6.3%)	5	4 (2.5%)	4	0 (0.0%)	0
WOUND ISSUES, OTHER	0	1	0	4	3	0	1	1	0	2	0	1	7 (8.8%)	7	5 (3.1%)	5	1 (2.0%)	1

Patients may have adverse events in more than one category and are counted once in each category in which they experience an adverse event
The "n" is the total number of patients treated, including patients with major protocol violations

[1] Four PRODISC®-L subjects reported adjacent level symptoms.

* Eight control subjects reported eight "Other" events: night sweats, lung cancer, thrombocytopenia, weight loss, increased liver enzymes, drowsiness, low magnesium, diabetes.

Eleven PRODISC®-L randomized subjects reported thirteen "Other" events: Factor V abnormality, concussion, diabetes (3), nose bleeds, gluteal hematoma, lung infiltrate, chills, low serum magnesium (2), tooth extraction, hot flashes.
Two PRODISC®-L non-randomized subjects reported two "Other" events: photophobia, trauma due to fall.

There is a statistically significant higher incidence of All Adverse Events in the randomized PRODISC®-L group compared to the non-randomized PRODISC®-L group. In the All Adverse Events "Pain Other (not back/hip/leg)" category, there is a statistically significant higher incidence in the randomized PRODISC®-L group compared to the non-randomized PRODISC®-L group.

The number of adverse events considered by the investigator to be device-related were less in the PRODISC®-L group (36/212, 17.0%) than in the control group (16/80, 20.0%); however, this was not statistically significant. **Table 4** lists all device-related adverse events that occurred in the PRODISC®-L Total Disc Replacement and control subjects.

Table 4: Device-related Adverse Events

	Fusion n=80		PRODISC®-L (Randomized) n=162		PRODISC®-L (Non-randomized) n=50	
	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
All Device Related Adverse Events	16 (20.0%)	34	29 (17.9%)	50	7 (14.0%)	15
Pain - Back	5 (6.3%)	6	8 (4.9%)	8	3 (6.0%)	3
Pain - Back and Lower Extremities	2 (2.5%)	2	6 (3.7%)	7	2 (4.0%)	2
Pain - Lower Extremities	4 (5.0%)	6	6 (3.7%)	6	0 (0.0%)	0
Numbness Peripheral Nerve or Non-Index Level Related	0 (0.0%)	0	4 (2.5%)	4	2 (4.0%)	2
Edema	0 (0.0%)	0	2 (1.2%)	2	0 (0.0%)	0
Other Musculoskeletal	3 (3.8%)	3	2 (1.2%)	2	1 (2.0%)	1
Burning or Dysesthetic Pain	0 (0.0%)	0	1 (0.6%)	1	1 (2.0%)	1
Degenerative Disease Progression, Other Lumbar	0 (0.0%)	0	3 (1.9%)	3	0 (0.0%)	0
Fracture (Non-Vertebral)	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Herniated Nucleus Pulposus	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Motor Deficit in Index Level	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Pain - Back and Lower Extremities with Burning	0 (0.0%)	0	1 (0.6%)	1	1 (2.0%)	1
Pain - Back and Lower Extremities with Numbness at Index Level	1 (1.3%)	2	1 (0.6%)	1	0 (0.0%)	0
Pain-Lower Extremities with Numbness at Index Level	0 (0.0%)	0	1 (0.6%)	1	1 (2.0%)	1
Musculoskeletal Spasms - Back	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
Nerve Root Injury	0 (0.0%)	0	0 (0.0%)	0	1 (2.0%)	1
Pain Other (not Back/Hip/Leg)	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
Radiolucency - Graft	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
Headache	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
Cardiovascular	2 (2.5%)	2	0 (0.0%)	0	0 (0.0%)	0
Gastrointestinal	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
Pruritus	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
Other	1 (1.3%)	1	0 (0.0%)	0	0 (0.0%)	0
Subsidence not Requiring Surgery	1 (1.3%)	1	2 (1.2%)	2	1 (2.0%)	1
Migration Requiring Surgery	0 (0.0%)	0	4 (2.5%)	4	0 (0.0%)	0
Migration not Requiring Surgery	1 (1.3%)	1	3 (1.9%)	3	2 (4.0%)	2

	Fusion n=80		PRODISC®-L (Randomized) n=162		PRODISC®-L (Non-randomized) n=50	
	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
Surgery - Index Level (Supplemental Fixation)	0 (0.0%)	0	1 (0.6%)	1	0 (0.0%)	0
Surgery - Index Level (Revision)	4 (5.0%)	4	1 (0.6%)	1	0 (0.0%)	0

Patients may have adverse events in more than one category and are counted in each category in which they experience an adverse event.

Device failures were those that required reoperation, revision, removal, or supplemental fixation. Device failures occurred in 6/212 (2.8%) PRODISC®-L and 2/80 (2.5%) control subjects; however, there is no statistically significant difference. In the PRODISC®-L group, four of these events (4/6) consisted of removal of the device followed by fusion of the treatment level after anterior migration of the PRODISC®-L. In the case of one of these subjects, the removal and fusion was subsequent to a prior attempted PRODISC®-L revision after anterior migration. Additionally, one PRODISC®-L subject underwent revision because the polyethylene inlay had been inserted backwards; and one PRODISC®-L subject underwent posterior supplemental fixation (fusion) for facet disease at the implanted level (the PRODISC®-L was found to be well positioned and solidly fixed, so it was left in place). Both of the device failures in the control group consisted of removal of hardware subsequent to pain.

The following potential adverse events (singly or in combination) which may be expected to occur, but were not observed in the clinical trial, could also result from the implantation of the PRODISC®-L Total Disc Replacement:

Surgery Related

- Anesthetic reaction
- Bowel perforation
- Epidural hematoma
- Hernia
- Ileus requiring nasogastric tube
- Infection – peritonitis
- Peritoneal adhesions
- Pulmonary embolism
- Retroperitoneal hematoma
- Seizures
- Injury to kidneys or ureters
- Nerve damage due to surgical trauma or presence of the device, neurological difficulties, including bowel and/or bladder dysfunction, impotence, tethering of nerves in scar tissue, muscle weakness or paresthesias
- Vascular damage resulting in catastrophic or fatal bleeding
- Paralysis
- Damage to lymphatic vessels and/or lymphatic fluid exudation
- Fracture of vertebral bony structures
- Additional surgery which could include removal of the PRODISC®-L
- Failure of the device/procedure to improve symptoms and/or function

- Wear debris generation either plastic or metal leading to an adverse reaction of the local tissues that may lead to implant loosening or failure
- Death

Post Surgery
- Malpositioned implants adjacent to large arteries or veins could erode these vessels and cause catastrophic bleeding in the late postoperative period
- Expulsion or retropulsion of the device, potentially casing pain, paralysis, vascular or neurological damage, spinal cord impingement or damage
- Implant breakage, dislodgement, or migration
- Deterioration in neurologic status
- Reflex sympathetic dystrophy
- Spondylolysis
- Spondylolisthesis
- Spinal stenosis
- Change in lordosis
- Instability of the spine
- Facet joint degeneration
- Foreign body reaction
- Calcification resulting in bridging trabecular bone and fusion
- Annular ossification

IX. SUMMARY OF NONCLINICAL LABORATORY STUDIES

A series of mechanical tests were performed to characterize the properties and function of the PRODISC®-L Total Disc Replacement. The tests conducted were:

- Static compression shear test
- Dynamic compression shear test
- Creep-relaxation test
- Static polyethylene inlay push-out test
- Dynamic polyethylene inlay push-out test
- Wear test
- Hysteresis test
- Expulsion test

For all tests, except where noted, samples of the following test constructs were utilized:

Table 5: Test Sample Components

Sample	Component	Quantity
PRODISC®-L – 10mm	Superior plate size M, 6°, for 10mm height	1
	Polyethylene inlay size M, for 10mm disc height	1
	Inferior plate size M	1
PRODISC®-L – 14mm	Superior plate size M, 6°, for 14mm height	1
	Polyethylene inlay size M, for 14mm disc height	1
	Inferior plate size M	1

Of the samples tested, the PRODISC®-L – 14mm construct represents a worse case scenario. This construct utilizes the smallest plate size (M) available, as well as the tallest polyethylene inlay with the smallest surface area.

Static Compression Shear Test

Sterilized samples were tested in static compression shear in ambient air (20°C) in a Zwick 1485 machine. Test samples were kept in a 37°C water bath until just before the test run. Samples were tested in 10° flexion and 5° extension (the flexion/extension angles were incorporated in the superior test fixture). Axial load was applied at a rate of 1mm/min. The test was stopped at gross failure of the implant, 5mm displacement of the actuator, or maximum load capacity of the test machine (25kN).

Table 6: Flexion (10°) Test Results

Implant	Samples	Mean Ultimate Force (N, S.D.)	Displacement at Ultimate Force (mm, S.D.)
PRODISC®-L – 10mm	6	8625 ± 308	3.34 ± 0.38
PRODISC®-L – 14mm	6	7800 ± 191	2.80 ± 0.11

Table 7: Extension (-5°) Test Results

Implant	Samples	Mean Ultimate Force (N ± S.D.)	Displacement at Ultimate Force (mm ± S.D.)
PRODISC®-L – 10mm	6	18,883 ± 930	1.47 ± 0.07
PRODISC®-L – 14mm	6	19,617 ± 334	3.00 ± 0.05

All samples tested in flexion failed due to shearing of the implant off the polyethylene inlay. All samples tested in extension failed due to shearing of the snap-in feature of the polyethylene inlay and expulsion of the inlay anteriorly. The static loads at which these failures occur are much higher than the expected static *in vivo* loads; and these loads likely would not be experienced *in vivo* at shear angles greater than 10°.

Dynamic Compression Shear Test

Fourteen sterilized samples were tested in dynamic compression shear in saline solution (0.9% at 37°C). Test samples were kept in a 37°C saline bath until just before the test run. The metal endplates were bonded to the test blocks with adhesive. Polyethylene inlay samples were tested with a 10° shear angle to the horizontal. Axial load was applied with a load ratio of R=10 and frequency of 10Hz out to 10 million cycles or failure. Failure was defined as 2mm maximum displacement or metal-to-metal contact of the endplates.

Test results showed that the polyethylene inlays for the PRODISC®-L – 10mm and PRODISC®-L – 14mm remained functional after 10 million cycles at 3.114 kN and 2.669 kN. respectively. These loads are within the range of expected *in vivo* lumbar loads.

Creep

Twelve sterilized samples were evaluated for creep performance of the UHMWPE. A 38-hour. 7-stage loading regimen that included both static and dynamic loads (1 Hz) was used. Testing occurred in saline solution (0.9% at 37°C). Test samples were kept in a 37°C saline bath until just before the test run. The metal endplates were bonded to the test blocks with adhesive.

Polyethylene inlay samples were tested with a 10° shear angle to the horizontal. The test was stopped following completion of the 38-hour loading sequence, 2mm of displacement, or failure of the implant.

The seven phases of loading were: static 300N load (3 hours), dynamic 300-1000N load (3 hours), static 300N load (2 hours), dynamic 300-2000N load (6 hours), static 300N load (4 hours), dynamic 300-3000N load (12 hours), and static 300N load (8 hours). The loading mode was meant to represent the typical daily loading on the lumbar spine as a result of sleeping, walking, sitting, etc. At the end of each phase, the displacement of the device was measured to evaluate creep behavior.

Test results showed that the polyethylene inlays for the PRODISC®-L – 10mm and PRODISC®-L – 14mm exhibited a residual deformation of 0.345mm and 0.349mm, respectively. Although the loads employed may not have been representative of a worse case scenario, the magnitude and duration of the dynamic loads employed are representative of what would be expected *in vivo*. Further, with the low residual deformation, failure due to creep is unlikely.

Static Inlay Push-out Test

Six samples each of four sizes of PRODISC®-L UHMWPE inlays (M – 10mm, M – 14mm, L – 10 mm, and L – 14mm) were tested by inserting the inlay into the equally-sized inferior metal endplate, and then applying an anterior shear load to the posterior face of the inlay until failure. The load was applied at a rate of 1 mm/min, and testing was conducted in room temperature air. after presoaking the samples in a 37°C water bath.

Table 8: Static Inlay Push-out Test Results

Implant	Samples	Mean Ultimate Force (N ± S.D.)	Displacement at Ultimate Force (mm ± S.D.)
PRODISC®-L – M – 10mm	6	911 ± 15	2.43 ± 0.08
PRODISC®-L – M – 14mm	6	1105 ± 19	3.02 ± 0.04
PRODISC®-L – L – 10mm	6	875 ± 19	2.24 ± 0.07
PRODISC®-L – L – 14mm	6	896 ± 45	2.09 ± 0.15

Failure occurred in all test samples due to shear failure of the snap-in features of the UHMWPE inlays. The loads at which failures occurred are greater than the expected *in vivo* lumbar shear loads.

Dynamic Inlay Push-out Test

Using the same setup employed in the static inlay push-out testing, six samples each of four sizes of PRODISC®-L UHMWPE inlays were tested to establish the maximum dynamic run-out load to 10 million cycles. A dynamic, anteriorly-directed pure shear force was applied to the posterior surface of the polyethylene inlay with a load ratio of R=10. Testing was conducted in a 37°C saline solution. The test frequency varied between 1Hz and 10 Hz. Testing stopped at gross failure of the implant, when the maximum load capacity of the test machine was reached. disengagement of the inlay, or run out.

Table 9: Dynamic Inlay Push-out Test Results

Implant	Samples	Endurance Limit (N)
PRODISC®-L – M – 10mm	7	500
PRODISC®-L – M – 14mm	6	500
PRODISC®-L – L – 10mm	6	500
PRODISC®-L – L – 14mm	6	600

Failure occurred in all test samples due to shear failure of the snap-in features of the UHMWPE inlays. The results of these tests suggest that failure of the UHMWPE inlay may occur at dynamic loads less than those predicted by the dynamic shear compression testing. However, *in vivo* shear forces of ≥ 500N are not expected during normal activity.

Wear Test

Wear testing was conducted to characterize the wear behavior of the PRODISC®-L Total Disc Replacement. Testing was conducted on six samples of the PRODISC®-L – 14mm constructs. The specimens were placed in the testing machine at a 10° angle from the horizontal to induce a shear load component. The test fluid was 37°C bovine calf serum. Devices were tested in combined flexion-extension (+6°/-3° at 1.1 Hz), lateral bending (±2° at 1.05 Hz), and axial rotation (±1.5° at 1.16 Hz). A sinusoidal compressive load ranging from 300 to 1750N was applied at a frequency of 1.57 Hz. Because of the different frequencies for the different motions, tests were carried out to 10 million cycles of flexion-extension, resulting in 14.28 million compressive loading cycles. Specimens were weighed at various time intervals to calculate wear rate, and wear debris samples were collected after 2 million, 5 million, 7 million, 8 million, 9 million, and 10 million cycles.

Linear interpolation of the wear rates of all test specimens results in a mean wear rate of 5.73mg/million cycles for a total average wear rate of 57mg over 10 million cycles. Initial wear rates (0-2 million cycles) tended to be higher than the later wear rates (2-10 million cycles). Mean particle diameter was 0.44μm with sizes ranging from of 0.08 to 2.29μm. Particle morphologies tended to be globular/granular in earlier cycles and slightly elongated/ flake-like in later cycles.

The results from the wear study suggest that the device will generate wear debris at expected lumbar loads. An evaluation of the human response to wear debris is presented in the Biocompatibility section of this document.

Hysteresis Test

Hysteresis testing was conducted to evaluate the amount of permanent deformation. Six specimens were tested by applying a dynamic load (300-3600 N) at a low frequency (0.1 Hz) for 2000 cycles and measuring the stiffness and hysteresis of the UHMWPE inlay every 100 cycles. Testing was performed in a 37°C water bath. The test was stopped after 2000 cycles or when 2mm of displacement was achieved.

Four specimens achieved run out to 2000 cycles. Two specimens failed as a result of reaching the 2mm displacement limit due to plastic deformation of the UHMWPE inlay. No fractures were observed. The results of this test indicate that while some deformation may be observed at high loads, no functional failure of the device occurred. However, the loads employed in this

test exceed the expected *in vivo* lumbar loads; and therefore, failure as a result of hysteresis is not expected.

Expulsion Test

The purpose of this test was to evaluate the mechanical fixation of the whole implant when subjected to a static shear load. Six samples were placed in polyurethane foam blocks and then subjected to an anteriorly-directed shear force until the sample was expelled from the foam blocks or displaced 5mm. A static compressive preload of 450N was applied while the shear load was applied at a rate of 5 mm/min. Testing was conducted in ambient air.

Table 10: Expulsion Test Results

Implant	Samples	Mean Shear Force (N ± S.D.)	Mean Displacement (mm ± S.D.)
PRODISC®-L – M	3	636 ± 82	1.17 ± 0.24
PRODISC®-L – L	3	685 ± 93	1.40 ± 0.22

The results of these tests suggest that the device can be expelled from the disc space at shear loads greater than 600N. However, *in vivo* shear forces of ≥ 500N are not expected during normal activity.

Biocompatibility

The endplates are constructed of CoCrMo alloy that conforms to ISO 5832-4 and ASTM F-75. The UHMWPE inlay conforms to ISO 5834-2 and ASTM F-648. These materials have a long history of use in medical implants with no significant biocompatibility issues.

To further characterize the biological response to UHMWPE wear debris, data from the wear test were compared to the data from a biological reaction study using UHMWPE particulate in a rabbit model (Cunningham, BW. Spine J. 2004 Nov-Dec;4(6 Suppl):219S-230S). The material, size distribution, and morphology of the UHMMPE particles used in the study are similar to that generated by the PRODISC®-L. The amount of wear debris used in the Cunningham study exceeds by three times what would be expected in a PRODISC®-L patient with forty years of implantation. (Cunningham used 3 mg of wear debris in a 5 kg rabbit, which would be comparable to 45 mg in a 75 kg patient.) In ten million cycles, the PRODISC®-L, in the worst case *in vitro* wear testing, produces 57 mg of wear debris, less than the 60 mg equivalent test dose used in the animals.

The conclusion of the Cunningham study was that no evidence was seen of an acute neural or systemic histopathologic response to the UHMWPE particles. Therefore, no negative biological response is expected from the wear generated by the PRODISC®-L Total Disc Replacement.

X. SUMMARY OF CLINICAL STUDIES

Study Objectives

Clinical data were collected to evaluate the safety and effectiveness of the PRODISC®-L Total Disc Replacement as compared to the control device, a circumferential fusion (interbody fusion using a commercially available femoral ring allograft, posterolateral fusion with autogenous iliac crest bone graft, and pedicle screw instrumentation). The purpose of the study was to demonstrate the non-inferiority of the PRODISC®-L Total Disc Replacement to circumferential fusion.

Study Design

A multicenter, prospective, randomized, controlled clinical trial was conducted consisting of subjects with single-level Degenerative Disc Disease (DDD) between L3 and S1 who had not previously received prior fusion surgery at any vertebral level, and had failed to improve with conservative treatment for at least 6 months prior to enrollment. Subjects were randomized to receive either the PRODISC®-L Total Disc Replacement or a circumferential fusion. Prior to randomization of the study subjects, the first three subjects enrolled at each investigational site were implanted with the PRODISC®-L Total Disc Replacement for the purpose of surgeon training (for a total of 50 non-randomized subjects). Subjects were randomized using a two to one ratio of PRODISC®-L recipients to control recipients. Blocking techniques (fixed block size of six) were used to ensure a balance between the treatment groups at each center.

All subjects randomized to receive the PRODISC®-L Total Disc Replacement first underwent discectomy to remove the damaged disc and were implanted with the device in the same procedure (no other instrumentation was used to secure the device in position). The circumferential fusion group was used as the control group for this study. Subjects randomized to the control group underwent circumferential fusion, consisting of interbody fusion using a commercially available femoral ring allograft, posterolateral fusion with autogenous iliac crest bone graft, and pedicle screw instrumentation.

Safety and effectiveness was assessed in all randomized subjects. The applicant proposed that an individual subject be considered a study success (i.e., Overall Success) if all of the following conditions were met:

- improvement in the Oswestry Disability Index (ODI) ≥ 15% at 24 months compared to the score at baseline
- no re-operation required to remove or modify the PRODISC®-L implant (investigational group) or to modify the fusion site or correct a complication with an implant (control group)
- improvement in Short Form-36 (SF-36) (i.e., 24-month score – pre-operative score > 0)
- neurological status improved or maintained (motor, sensory, reflex, straight leg raise)
- radiographic success.

Radiographic success in the investigational group was defined by the applicant as:

- no radiographic evidence of device migration or subsidence > 3mm
- no extensive radiolucency along the implant/bone interface (< 25% of the interface's length for each endplate defined as a success)

- range of motion (ROM) at the implanted level will be maintained or improved from the pre-operative baseline
- no loss of disc height > 3mm
- no evidence of bony fusion.

Radiographic success in the control group was defined by the applicant as:
- no radiographic evidence of device migration or subsidence > 3mm
- no implant loosening (no halos or radiolucencies around the implant)
- no motion on flexion/extension films (success defined as < 3mm translation and < 5° angulation)
- no loss of disc height > 3mm
- strong evidence of fusion, including > 50% trabecular bridging bone or bone mass maturation and increased or maintained bone density at the site
- no visible gaps in the fusion mass.

Based on lumbar flexion/extension ranges of motion cited in the literature, the applicant considered PRODISC®-L subjects a success in terms of "ROM at the implanted level maintained or improved" if the flexion/extension ROM at 24 months was "normal", where "normal" ROM was defined as follows:
- L3/L4 normal if ROM ≥ 6° (with ± 3° measurement error applied) and ≤ 20° (device design limit)
- L4/L5 normal if ≥ 6° (with ± 3° measurement error applied) and ≤ 20° (device design limit)
- L5/S1 normal if ≥ 5° (with ± 3° measurement error applied) and ≤ 20° (device design limit).

The applicant considered the study a success if at 24 months the overall success rate of the investigational group was not inferior to that of the overall success rate of the control group; and the device related complication rate (including subsequent surgical interventions and neurological complications) of the investigational group was not inferior to that of the control group. The margin for establishing non-inferiority was proposed as 12.5%.

FDA requested that the data also be analyzed and reported using the following criteria:
- improvement in the ODI score ≥ 15 points at 24 months compared to the score at baseline
- maintenance or improvement of ROM defined as (24 month flexion/extension ROM – Pre-operative flexion/extension ROM) ≥ 0 (with ± 3° measurement error applied)
- a non-inferiority margin of 10%.

Inclusion/Exclusion criteria

To qualify for enrollment in the study, subjects met all the inclusion criteria and none of the exclusion criteria listed in the following table:

Table 11: Inclusion/Exclusion Criteria

Inclusion	Exclusion
▪ Degenerative Disc Disease (DDD) in one vertebral level between L3 and S1. Diagnosis of DDD requires back and/or leg (radicular pain); and radiographic confirmation of any 1 of the following by CT, MRI, discography, plain film, myelography and/or flexion/extension films: o Instability (≥ 3mm translation or ≥ 5° angulation); o Decreased disc height > 2mm; o Scarring/thickening of annulus fibrosis; o Herniated nucleus pulposus; or o Vacuum phenomenon ▪ Age between 18 and 60 years ▪ Failed at least 6 months of conservative treatment ▪ Oswestry Low Back Pain Disability Questionnaire score of at least 20/50 (40%) (Interpreted as moderate/severe disability) ▪ Psychosocially, mentally and physically able to fully comply with this protocol including adhering to follow-up schedule and requirements and filling out of forms ▪ Signed informed consent	▪ No more than 1 vertebral level may have DDD, and all diseased levels must be treated ▪ Patients with involved vertebral endplates dimensionally smaller than 34.5 mm in the medial-lateral and/or 27 mm in the anterior-posterior directions ▪ Known allergy to titanium, polyethylene, cobalt, chromium or molybdenum ▪ Prior fusion surgery at any vertebral level ▪ Clinically compromised vertebral bodies at the affected level due to current or past trauma ▪ Radiographic confirmation of facet joint disease or degeneration ▪ Lytic spondylolisthesis or spinal stenosis ▪ Degenerative spondylolisthesis of grade > 1 ▪ Back or leg pain of unknown etiology ▪ Osteopenia or osteoporosis: A screening questionnaire for osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Estimation), will be used to screen patients to determine if a DEXA scan is required. If DEXA is required, exclusion will be defined as a DEXA bone density measured T score < -2.5. ▪ Paget's disease, osteomalacia or any other metabolic bone disease (excluding osteoporosis which is addressed above) ▪ Morbid obesity defined as a body mass index > 40 or a weight more than 100 lbs. over ideal body weight ▪ Pregnant or interested in becoming pregnant in the next 3 years ▪ Active infection – systemic or local ▪ Taking medications or any drug known to potentially interfere with bone/soft tissue healing (e.g., steroids) ▪ Rheumatoid arthritis or other autoimmune disease ▪ Systemic disease including AIDS, HIV, Hepatitis ▪ Active malignancy: A patient with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she has been treated with curative intent and there has been no clinical signs or symptoms of the malignancy for at least 5 years

Post-operative Care

Following surgery, while investigators were advised to prescribe the appropriate rehabilitation program and manage its progress on a case-by-case basis, they were given certain guidelines to follow irrespective of the subject's treatment group. The guidelines included ambulation

beginning on postoperative day 1-3 with supervised use of a walker and a simple corset when out of bed (at the surgeon's discretion). Isometric leg exercises were recommended for the first two weeks postoperatively with the subsequent initiation of outpatient physical therapy. The guidelines suggested that subjects be instructed to avoid excessive bending or lifting for the first two weeks postoperatively; to begin driving, light bending, and lifting from 2-6 weeks postoperatively; and to gradually resume normal activities beginning at 6 weeks postoperatively. The goal of the rehabilitation program was to return the subject to normal activity as soon as possible without jeopardizing the healing process, irrespective of treatment.

Clinical and radiographic effectiveness parameters

Subjects were evaluated preoperatively, intraoperatively, and immediately postoperatively followed by evaluations at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial.

Overall Success was determined from data collected during the initial 24 months of follow-up. Primary outcome parameters were evaluated for all treated subjects at 6, 12, 18 and 24 months using both the applicant's proposed success criteria and FDA's requested definition of Overall Success, as described previously.

Neurological status was a global assessment that incorporated information from the following: (i) reflexes at the knee and ankle (absent/present, symmetrical/asymmetrical); (ii) motor function (bilateral or unilateral weakness, evaluated on a 5-point scale for gluteus maximus, iliopsoas, quadriceps, hamstrings, anterior tibial group, posterior tibial, extensor hallucis longus, and flexor hallucis); (iii) sensitivity to light touch (numbness, tingling in the groin, anterior thigh, medial leg, lateral leg, and lateral foot); and (iv) straight leg raise, with evaluation of cross-positive reactions.

Secondary endpoints assessed included:

- Oswestry Disability Index (ODI) (using ≥ 25%, ≥ 15%, and ≥ 15 points improvement from baseline)
- Visual Analog Scale (VAS) pain (improvement comparing baseline and 24-month post-operative scores; no definition of success provided)
- Visual Analog Scale (VAS) satisfaction
- Neurological Assessment (motor, sensory, reflex, straight leg raise)
- Quality of life (SF-36) (improvement of 15% at 24 months compared to baseline)
- Willingness to have the same surgery again
- Radiographic assessments including:
    - Implant migration (> 3mm)
    - Subsidence (> 3mm)
    - Radiolucency along the implant/bone interface (>25% of the interface's length for each endplate in the investigational group; halos or radiolucencies around the implant in the control group)
    - Loss of disc height (> 3mm)
    - Motion status at the implanted level
    - Fusion status at the implanted level

Safety of the PRODISC®-L Total Disc Replacement was assessed by monitoring intra-operative and postoperative complications. Radiographs were used to monitor the occurrence of some of the adverse events and complications, including subsidence of the device into the adjacent disc, device migration, other changes in the implant, and spinal instability.

All radiographic endpoints were evaluated independently by a core laboratory and reviewed by an independent radiologist.

Subject Accountability and Demographics

Seventeen (17) sites participated in the study with a total of two hundred ninety two (292) subjects enrolled and treated; the first three subjects at each center were not randomized and served as training cases. 162 subjects in the randomized treatment arm (PRODISC®-L randomized), 80 subjects in the control arm (circumferential fusion), and 50 subjects in the non-randomized treatment arm (PRODISC®-L non-randomized) were treated.

Table 12 below provides an account of all subjects enrolled and treated in the study who completed all evaluations at each time point within the windows defined in the approved investigational protocol.

Table 12: Patient Accountability

	Preop			6 wks			3 mo			6 mo			12 mo			18 mo			24 mo		
	F	P-R	P-NR	F	P-R	P-NR	F	P-R	P-NR	F	P-R	P-NR	F	P-R	P-NR	F	P-R	P-NR	F	P-R	P-NR
Enrolled	93	183	51	93	183	51	93	183	51	93	183	51	93	183	51	93	183	51	93	183	51
Treated	80	162	50	80	162	50	80	162	50	80	162	50	80	162	50	80	162	50	80	162	50
Theoretical	80	162	50	80	162	50	80	162	50	80	162	50	80	162	50	80	162	50	80	162	50
Deaths (cumulative)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Failures (cumulative)	0	0	0	0	2	0	0	3	0	0	3	0	0	3	0	2	4	0	2	6	0
Not yet overdue	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Expected	80	162	50	80	160	50	80	159	50	80	159	50	80	159	50	78	158	50	78	156	50
Evaluated	75	161	50	73	155	50	71	152	50	70	150	50	62	139	48	52	130	44	71	149	48
Actual*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	56	122	41	46	116	37	69	142	45
Follow-up rate (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	70.0%	76.7%	82.0%	59.0%	73.4%	74.0%	88.5%	91.0%	90.0%
Actual* (in window)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	54	114	37	41	105	34	57	124	35
Follow-up rate (In window %)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	67.5%	71.7%	74.0%	52.6%	66.5%	68.0%	73.1%	79.5%	70.0%

*Radiographic data at these timepoints were not assessed because 1) there is no expectation of bone bridging to occur in the early post-operative period therefore it is not assessed prior to 12 months and 2) F/E ROM radiographs are not generally taken prior to 6 months to avoid disruption of the fusion mass or implant fixation 3) Due to the short time from surgery Migration/Subsidence/Radiolucency cannot be adequately assessed until the 3 month visit.

Several analyses were performed to assess whether PRODISC®-L's treatment effect is consistent across different sites using the sponsor's proposed and FDA's requested definitions of Overall Success. Pooling of the data across the sites within a given group of subjects is inconclusive.

Table 13 below shows the demographics and baseline characteristics of the investigational and control groups. There were no statistically significant differences between the study groups.

Table 13: Demographic and Baseline Characteristics

	Fusion (n =80)	PRODISC®-L (Randomized) (n=162)	p-value		PRODISC®-L (Non-randomized) (n=50)
Age at Surgery (years)			0.2132		
N	80	162			50
Mean (SD)	40.2 (7.6)	39.6 (8.0)			37.9 (8.0)
Gender [N (%)]			0.5102		
Male	37 (46.3%)	83 (51.2%)			20 (40.0%)
Female	43 (53.8%)	79 (48.8%)			30 (60.0%)
Race [N (%)]			0.5118		
Caucasian	61 (76.3%)	133 (82.1%)			46 (92.0%)
African-American	6 (7.5%)	5 (3.1%)			2 (4.0%)
Hispanic	12 (15.0%)	19 (11.7%)			2 (4.0%)
Asian-American	0 (0.0%)	2 (1.2%)			0 (0.0%)
Other	1 (1.3%)	3 (1.9%)			0 (0.0%)
Smoking Status			0.2101		
Never	37 (46.3%)	87 (53.7%)			27 (54.0%)
Former	19 (23.8%)	41 (25.3%)			12 (24.0%)
Current	24 (30.0%)	34 (21.0%)			11 (22.0%)
Body Mass Index (kg/m²)			0.4855		
N	80	162			49
Mean (SD)	27.4 (4.3)	26.7 (4.2)			25.9 (4.6)
Baseline Oswestry Score (/ 100)			0.4979		
N	80	162			50
Mean (SD)	62.9 (63.4)	63.4 (12.6)			62.6 (11.9)
Target Level at Screening			0.6612		
L3-L4	3 (3.8%)	3 (1.9%)			1 (2.0%)
L4-L5	27 (33.8%)	54 (33.3%)			14 (28.0%)
L5-S1	50 (62.5%)	105 (64.8%)			35 (70.0%)
Prior Surgical Treatment			0.5503		
Any	24(30.0%)	57 (35.2%)			24 (48.0%)
Discectomy	14 (17.5%)	26 (16.0%)			11 (22.0%)
IDET	5 (6.3%)	18 (11.1%)			7 (14.0%)
Laminectomy	5 (6.3%)	15 (9.3%)			8 (16.0%)
Laminotomy	3 (3.8%)	4 (2.5%)			1 (2.0%)
Other	4 (5.0%)	12 (7.4%)			6 (12.0%)
Baseline Pain VAS			0.4848		
N	78	159			50
Mean (SD)	73.2 (14.5)	75.1(16.4)			72 (18.0)
Pre-operative Activity Level			0.3377		
None	40 (50.0%)	94 (58.0%)			30 (60%)
Light	35 (43.8%)	59 (36.4%)			17 (34%)
Non-contact sport	3 (3.8%)	6 (3.7%)			3 (6%)
Contact sport	0 (0.0%)	1 (0.6%)			0 (0%)
Other	2 (2.5%)	2 (1.2%)			0 (0%)

Surgical and Hospitalization Information

The mean intra-operative time was significantly shorter in the PRODISC®-L randomized group compared with the control group (121 minutes versus 219 minutes, p<0.0001). The mean estimated blood loss (EBL) was lower in the PRODISC®-L randomized group, compared with the control group (203 cc versus 451 cc, p<0.0001). The length of hospital stay was also statistically significantly shorter in the PRODISC®-L randomized group (3.5 days versus 4.4 days, p<0.0001) compared to the control group. While the differences in the means for each of these parameters were statistically significant, in each case, the ranges were similar so the statistical significance may not be clinically significant.

Table 14: Intra-operative and Hospital Data

	Fusion	PRODISC®-L (Randomized)	p-value*		PRODISC®-L (Non-randomized)
Implant Size			N/A		
N	80	162			50
Medium	N/A	118 (72.8%)			39 (78.0%)
Large	N/A	44 (27.2%)			11 (22.0%)
Intra-operative Time (Minutes)			<0.0001		
N	80	161			50
min-max	96 - 498	47 - 324			54 - 263
Mean (SD)	218.6 (75.9)	120.8 (59.2)			125 (46.1)
Estimated Blood Loss (cc)			<0.0001		
N	78	161			50
min-max	0 - 2200	0 - 1500			30 - 800
Mean (SD)	451 (434.2)	203 (230.3)			189 (155.3)
Surgical Approach			N/A		
N	80	162			50
Transperitoneal	2 (2.5%)	2 (1.2%)			2 (4.0%)
Retroperitoneal	62 (77.5%)	160 (98.8%)			48 (96.0%)
Posterior	41 (51.3%)	0 (0.0%)			0 (0.0%)
Length of Hospital Stay (Days)			<0.0001		
N	80	162			50
min-max	2.0 – 9.0	1.0 – 8.0			1.0 – 8.0
Mean (SD)	4.4 (1.54)	3.5 (1.29)			3.4 (1.39)

Clinical effectiveness outcomes

The primary effectiveness endpoint of this study was the difference in proportion of Overall Success between the two treatment groups. The success status of subjects was summarized by treatment groups.

Table 15 compares the success rates for the individual primary outcome parameters for all randomized subjects, as well as the Overall Success rates, using both the Applicant's proposed and FDA's requested success criteria for ODI improvement and ROM, and non-inferiority margins of 12.5% and 10%. Primary endpoint data were collected and analyzed 24-months after surgery.

The analysis population which was used to assess these endpoints consisted of all randomized subjects who completed all evaluations at the 24-month time point, regardless of when the 24-month measurement occurred.

Table 15: Components of Overall Success at Month 24

	Fusion	PRODISC®-L (Randomized)	PRODISC®-L (Non-randomized)
ODI success (≥15% improvement)	46/71 (64.8%)	115/149 (77.2%)	41/48 (85.4%)
ODI success (≥15 point improvement)	39/71 (54.9%)	101/149 (67.8%)	36/48 (75.0%)
Device success (no reoperation, revision, removal or supplemental fixation)	73/75 (97.3%)	155/161 (96.3%)	50/50 (100%)
Neurological success (maintain or improve – motor, sensory, reflex, and straight leg raise)	57/70 (81.4%)	135/148 (91.2%)	40/48 (83.3%)
SF-36 success (score improved)	49/70 (70.0%)	118/149 (79.2%)	43/48 (89.6%)
Radiographic success (using FDA's definition of ROM success)[1,5]	59/69 (85.5%)	125/143 (87.4%)	40/45 (88.9%)
Radiographic success (using Applicant's definition of ROM success)[2,5]	59/69 (85.5%)	131/143 (91.6%)	43/45 (95.6%)
Overall Success[3]	**32/71 (45.1%)**	**94/148 (63.5%)**	**30/45 (66.7%)**
Overall Success[4]	**29/71 (40.8%)**	**79/148 (53.4%)**	**25/45 (55.6%)**

1 (24 month flexion/extension ROM – Preop flexion/extension ROM) ≥ 0 (with ± 3° measurement error applied)

2 Flexion/extension ROM at 24 months "normal", where "normal" ROM defined as follows:
- L3/L4 normal if ROM ≥ 6° (with ± 3° measurement error applied) and ≤ 20° (device design limit)
- L4/L5 normal if ≥ 6° (with ± 3° measurement error applied) and ≤ 20° (device design limit)
- L5/S1 normal if ≥ 5° (with ± 3° measurement error applied) and ≤ 20° (device design limit)

3 Applicant proposed criteria: Analysis conducted per the investigational protocol, including ≥15% ODI score improvement, applicant's definition of ROM success, and a non-inferiority margin of 12.5%

4 FDA requested criteria: Analysis conducted as above, except: ≥15 point ODI score improvement, FDA's definition of ROM success, and a non-inferiority margin of 10%

5 Four of the patients had a partial post-24 month analyses and radiographic analysis was completed post 24 months (between 33 and 45 months post-operatively).

The 95% two-sided confidence interval indicates that the Overall Success rate for the PRODISC®-L Total Disc Replacement is within the non-inferiority margin, regardless of which set of study success criteria are used.

Although the study was not designed to show a difference, a statistically significant difference in Overall Success rates between the PRODISC®-L and control groups was found using a one-sided Fishers Exact Test, for both the applicant's proposed and FDA's requested definitions of Overall Success (p=0.0053 and p=0.0438, respectively).

Secondary endpoint outcomes

Mean ODI scores at baseline were similar for the three treatment groups: 63.4 in the PRODISC®-L randomized group, 62.6 in the PRODISC®-L non-randomized group, and 62.2 in

the control group. The difference in mean ODI scores between the PRODISC®-L randomized and control groups at 24 months was not statistically significant.

Table 16: Time Course of Mean ODI Scores

	Week 6	Month 3	Month 6	Month 12	Month 18	Month 24
Fusion	41.5	36.4	36.0	35.6	34.7	34.5
PRODISC®-L (Randomized)	49.8	46.6	41.5	40.7	39.8	39.8

A decrease in ODI score compared with baseline indicates improvement.

All three treatment groups showed significant reduction in pain compared to baseline VAS scores at all post-operative time points. Between the randomized PRODISC®-L and fusion groups, the improvement in VAS pain scores was not statistically significant at any time point except at 3 months. The difference in VAS satisfaction scores was statistically significant at the 24-month time point, where the PRODISC®-L subjects scored higher than control subjects (77 and 67, respectively).

Neurological success was defined as maintenance or improvement for all four success criteria (motor status, sensory status, reflexes, and straight leg raises). The investigational and control groups had similar outcomes at all time points, with a statistically significant difference between the PRODISC®-L randomized and control groups at 24 months.

Table 17 below summarizes the findings of the radiographic assessments.

Table 17: Radiographic Assessments

	Fusion	PRODISC®-L (Randomized)	PRODISC®-L (Non-randomized)
Migration > 3mm	1/69 (1.4%)	3/149 (2.0%)	1/46 (2.2%)
Subsidence > 3mm	0/69 (0%)	1/149 (0.7%)	1/46 (2.2%)
Radiolucency[1]	1/69 (1.4%)	0/149 (0%)	0/46 (0%)
Loss of disc height > 3mm	5/69 (7.2%)	0/148 (0%)	0/46 (0%)
Fusion status[2]	67/69 (97.1%)	---	---
Non-fusion status[3]	---	149/149 (100%)	46/46 (100%)
Motion status[4]	68/69 (98.6%)	128/143 (89.5%)	41/45 (91.1%)
Motion status[5]	68/69 (98.6%)	134/143 (93.7%)	44/45 (97.8%)

1. Radiolucency along the implant/bone interface (>25% of the interface's length for each endplate in the investigational group; halos or radiolucencies around the implant in the control group)
2. Strong evidence of fusion, including >50% trabecular bridging bone or bone mass maturation and increased or maintained bone density at site
3. No fusion
4. Investigational group: maintenance or improvement of ROM defined as (24 month F/E ROM – Preop F/E ROM) ≥ 0 (with ± 3° measurement error applied)

Control group: no motion (<3mm translation, <5° angulation) on flexion/extension films

5. Investigational group: maintenance or improvement in ROM if the flexion/extension ROM at 24 months is normal, where normal ROM is defined as follows:
   - L3/L4 normal if ROM ≥ 6° (with ± 3° measurement error applied) and ≤ 20° (device design limit)
   - L4/L5 normal if ≥ 6° (with ± 3° measurement error applied) and ≤ 20° (device design limit)
   - L5/S1 normal if ≥ 5° (with ± 3° measurement error applied) and ≤ 20° (device design limit)

   Control group: no motion (<3mm translation, <5° angulation) on flexion/extension films

Flexion/extension ROM in degrees at the operative level, determined as the difference in Cobb measurements between dynamic flexion/extension lateral radiographs, was measured at 3, 6, 12, 18 and 24 months. **Table 18** shows the time course distribution of the mean flexion/extension ROM for all subjects.

Table 18: Time Course of Mean Flexion/Extension ROM

	Month 3	Month 6	Month 12	Month 18	Month 24
Fusion	1.0	0.9	0.9	0.8	0.7
PRODISC®-L (Randomized)	6.3	6.1	7.0	7.1	7.7
PRODISC®-L (Non-randomized)	6.3	7.4	7.0	7.1	8.8

FDA requested that the applicant provide histograms showing the range of ROM values recorded for all PRODISC®-L randomized subjects. These histograms used values obtained by rounding recorded ROM for each subject to the nearest integer.

Figure 1: Range of PRODISC®-L Randomized Flexion/Extension Range of Motion Over Time

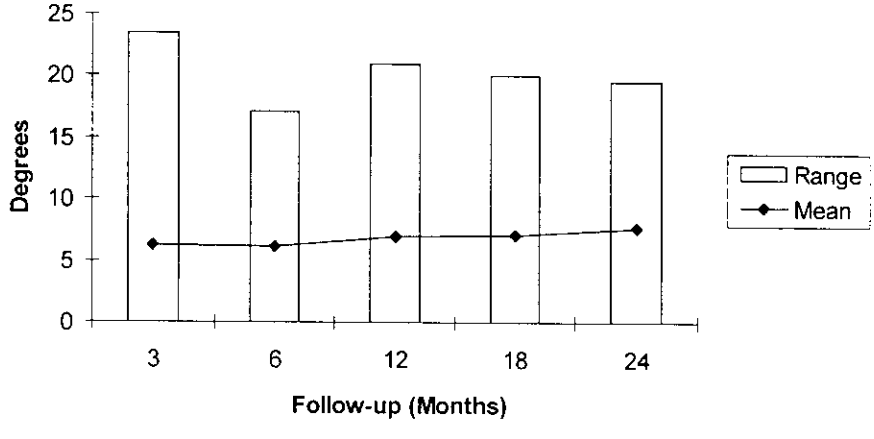
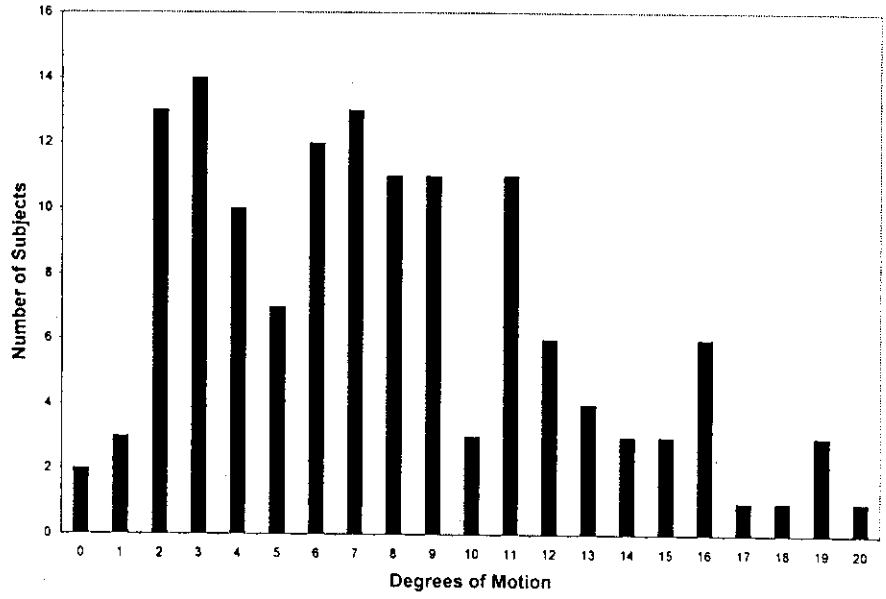


Figure 2: Histogram of PRODISC®-L Randomized Flexion/Extension Range of Motion at 24 Months



The applicant also analyzed range of motion data versus Overall Success for all PRODISC®-L subjects with available range of motion data at 24 months. No statistically significant association was found between range of motion and success/failure at 24 months.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The valid scientific evidence presented in the preceding sections demonstrates that the PRODISC®-L Total Disc Replacement is reasonably safe and effective by demonstrating its non-inferiority when comparing Overall Success and adverse event rates to the control for the studied indication.

XII. CDRH DECISION

CDRH approved the PRODISC®-L Total Disc Replacement based on the following:

- The overall incidence of adverse events occurring in the PRODISC®-L group was no worse than in the control group.
- The number of adverse events considered to be device-related in the PRODISC®-L group was no worse than in the control group.
- The Overall Success rate of the PRODISC®-L group was no worse than the Overall Success rate of the control group, with a non-inferiority margin of 10%, using FDA's criteria for Overall Success.

In order to gather long-term safety and effectiveness data, the applicant agreed to conduct a post-approval study to obtain a total of five-year follow-up data from all subjects in the clinical study. The post-approval study will utilize the same endpoints as the IDE clinical study. The post-approval study will also evaluate adjacent segment degeneration and the correlation of ROM

data with ODI and VAS scores. Because of the unknown long-term device performance, the post-approval study will include analysis of any retrieved implants returned to the applicant.

FDA worked with the applicant to review the content of the surgeon training program, to finalize product labeling, and to finalize the requirements of the post-approval study. The applicant's manufacturing facilities were inspected and found to be in compliance with the Quality System Regulation (21 CFR 820).

FDA issued an approval order on August 14, 2006.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions, and Adverse Reactions in the labeling.

Post Approval Requirements and Restrictions: See the Approval Order.